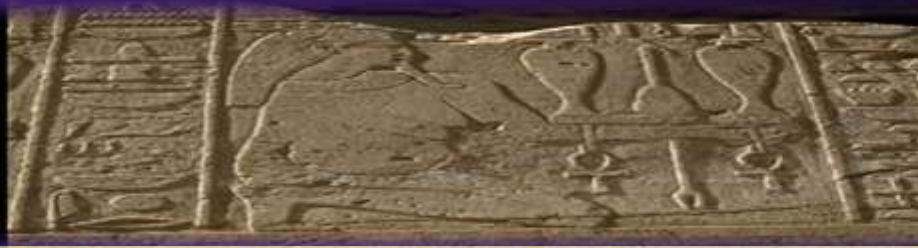


بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



# LEGAND BECOMES TRUTH

WHAT BEYONDS UK  
DIABETES DREAMS IN  
2014???

ISLAM EiD,MD  
MANSOURA UNIVESITY





# *At diagnosis*

**20 - 30%** Diabetic **eye** disease

**10 - 20%** Diabetic **Kidney** dysfunction

**30 - 40%** **hypertension**

**50 - 80%** **dyslipidemia**

**80 - 100%** **vascular** dysfunction



# THE LANCET

Volume 373 / Number 9669 / Pages 1053-1144 / March 28-April 3, 2009

[www.thelancet.com](http://www.thelancet.com)

"This epic study shows that obesity, as measured by BMI, is associated with increased total mortality in both men and women and in all age strata from 35 to 89 years."

See Comment page 1055

## Articles

Brachytherapy after resection of localized primary gastrointestinal stromal tumour

See page 1107

## Articles

Risk of epilepsy after traumatic brain injury

See page 1115

## Articles

Heart protection against toxemia after mass antibiotic distributions

See page 1121

## Seminars

Renal cell carcinoma

See page 1119

## Series

Health in the Occupied Palestinian Territory II: Human security

See page 1133

£5.00 Registered as a newspaper - ISSN 0140-6736  
Founded 1823 - Published weekly

## The Lancet

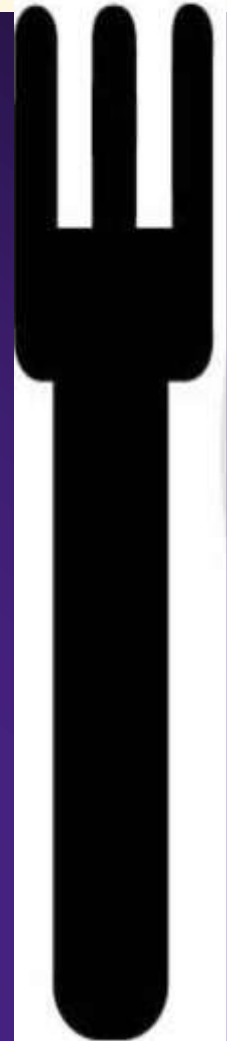
March 28<sup>th</sup> 2009

Body-mass index and cause-specific mortality in 900,000 adults: collaborative analysis of 57 prospective studies

BMI 30 – 35: 2-4 years of life lost

BMI 40 – 45: 8-10 years of life lost

# Carbohydrate junkies



# The Result?











# What is a low carbohydrate diet?

**‘ I don't think this is what the doctor meant by eating a low carbohydrate diet, honey.’**





Is There a Good  
News?

..the Good News is.....



## Surgery

### When to consider surgery

- Consider surgery for people with severe obesity if:
  - they have a BMI of  $40 \text{ kg/m}^2$  or more, or between  $35 \text{ kg/m}^2$  and  $40 \text{ kg/m}^2$  and other significant disease (for example, type 2 diabetes, high blood pressure) that could be improved if they lost weight
  - all appropriate non-surgical measures have failed to achieve or maintain adequate clinically beneficial weight loss for at least 6 months
  - they are receiving or will receive intensive specialist management
  - they are generally fit for anaesthesia and surgery
  - they commit to the need for long-term follow-up.
- Consider surgery as a first-line option for adults with a BMI of more than  $50 \text{ kg/m}^2$  in whom surgical intervention is considered appropriate; consider orlistat or sibutramine before surgery if the waiting time is long.





## Bariatric Surgery

- What is bariatric surgery?
- Perceived benefits for diabetes
- Risks and complications cohort study
- Long term



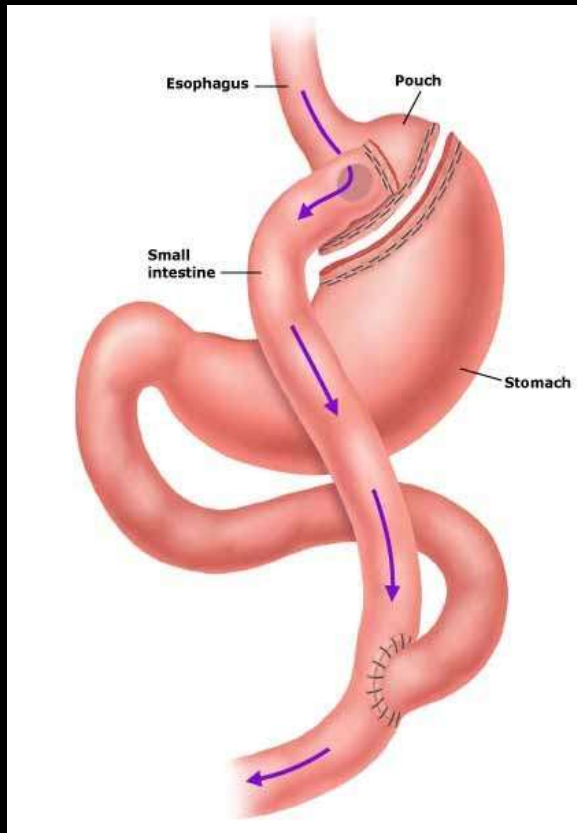


University of Glasgow | College of Medical,  
Veterinary & Life Sciences

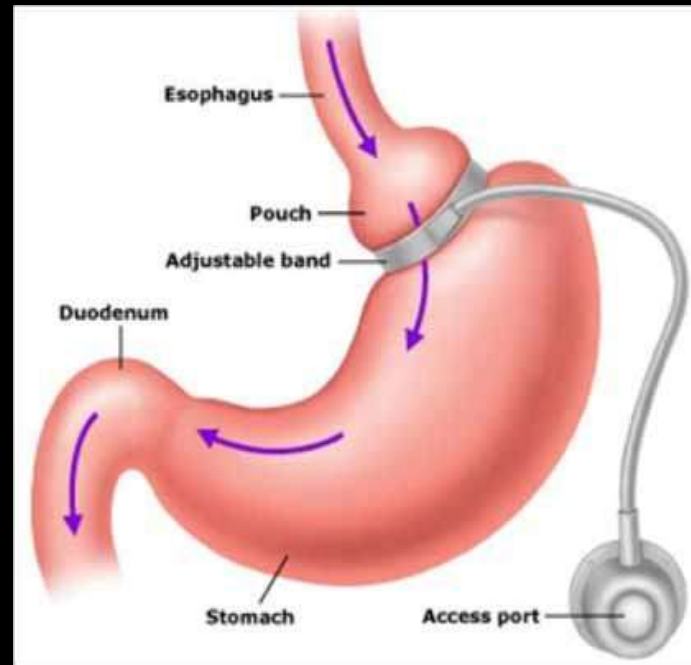


SurgiCal Obesity Treatment Study

# Bariatric operations



Roux-en-y-By pass

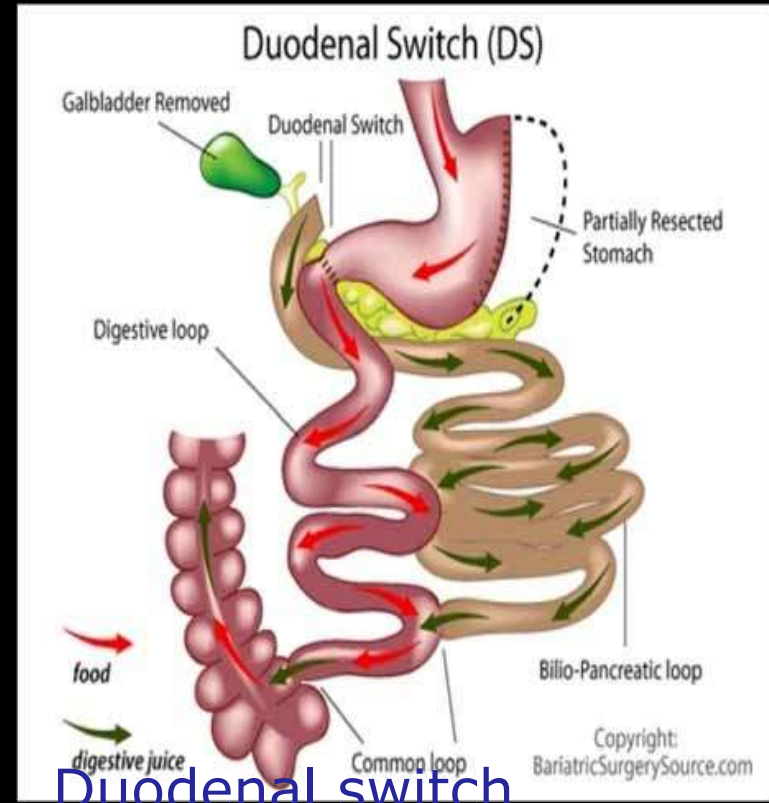
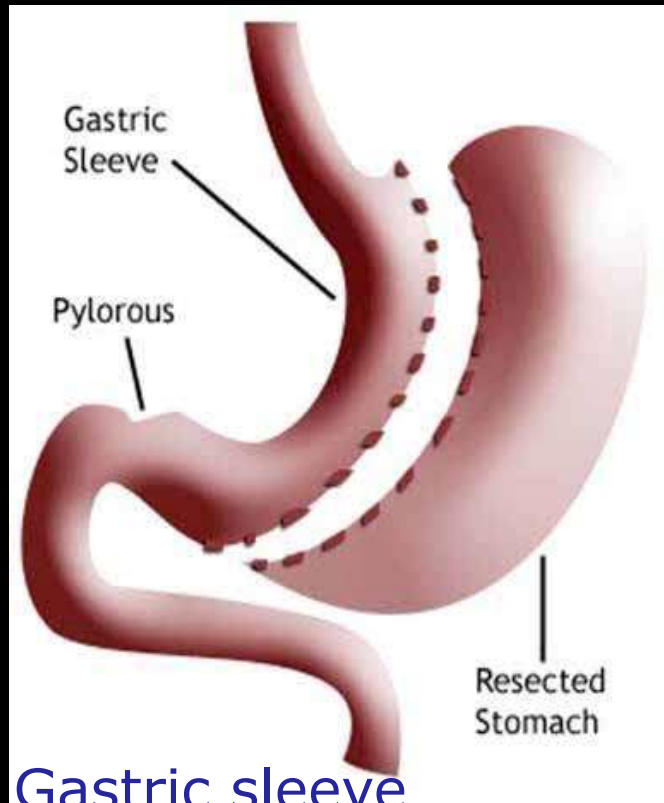


Gastric band





# Bariatric operations



# Mechanisms of bariatric surgery

Classical model:

**Mechanical**

**Malabsorption**

**Restricted food intake**



Current model:

**Metabolic**

**Altered GI signals to  
brain, liver, pancreas**

- Endocrine
- Neuronal



Stefater et al., *Endocrine Reviews*, 2012

# Diabetes and bariatric surgery

"My daddy is a doctor and he treats diabetes"

"My daddy is a surgeon and he cures it!"



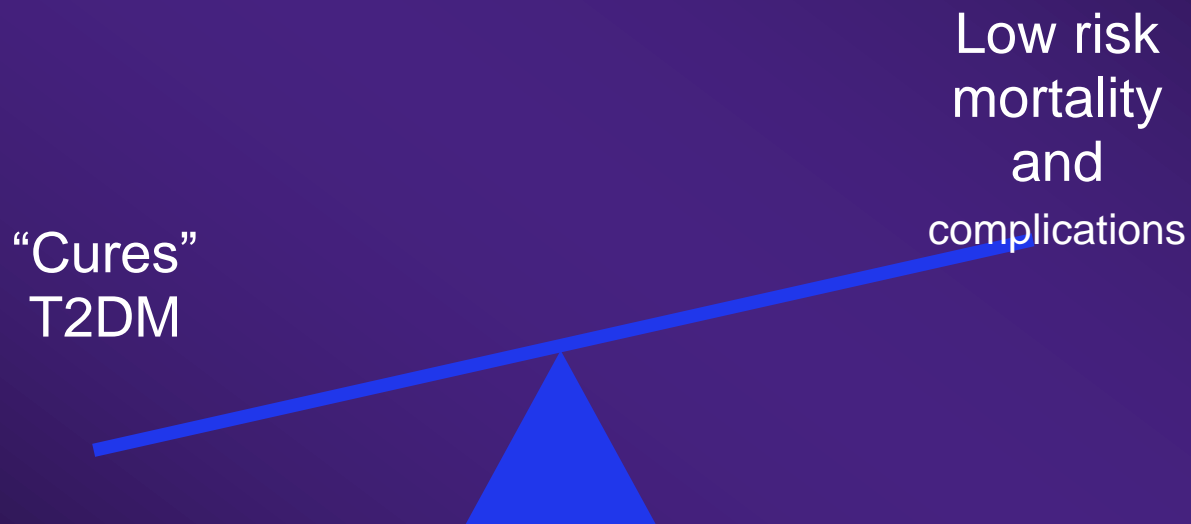






University  
of Glasgow

## The balance of benefits and risks



**Cost effective treatment for T2DM**



University  
of Glasgow

## The balance of benefits and risks

Improved  
glycaemic  
control  
& decreased  
medications

Low risk  
mortality  
and  
complications

Cost effective treatment for T2DM??





- ADA Definition:
  - HbA1c < 6% (42 mmol/mol)
  - fasting glucose less than 5.6 mmol/l
  - at least 1 year after bariatric surgery
  - without hypoglycaemic medication





University  
of Glasgow





University  
of Glasgow

# Micro and Macrovascular complications





University  
of Glasgow

**Would bariatric  
surgery  
still reduce CV  
events in  
T2DM in 2014?**





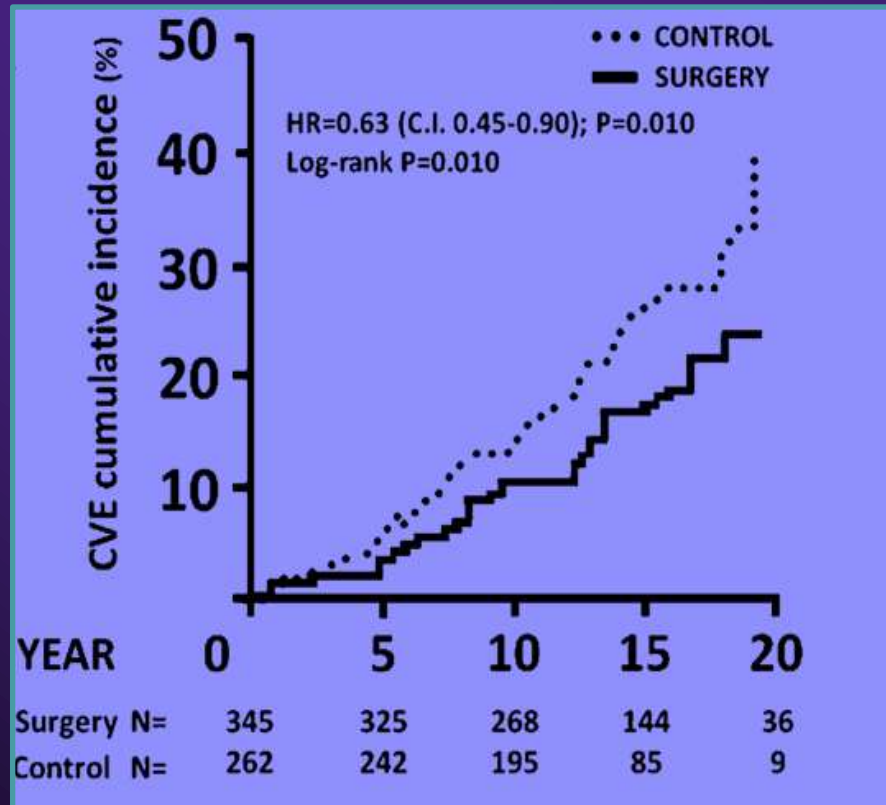
## SOS diabetes: prediction of benefit

- Those with higher baseline lipids (total cholesterol and triglycerides) had greatest benefit **NB** low statin use at baseline
- Those with higher fasting insulin also had greater benefit

Benefit present in those with BMI  $> 40$  and  $< 40$

- Diabetes complications – greatest benefit in newly diagnosed, **IDF 2013**.





- Median FU 14.7y
- 345 surgery (63 ev)
- 262 control (62 ev)
- **47% ↓ risk CV ev**
- **44% ↓ risk MI**



**Nephropathy – evidence of ↓dialysis**

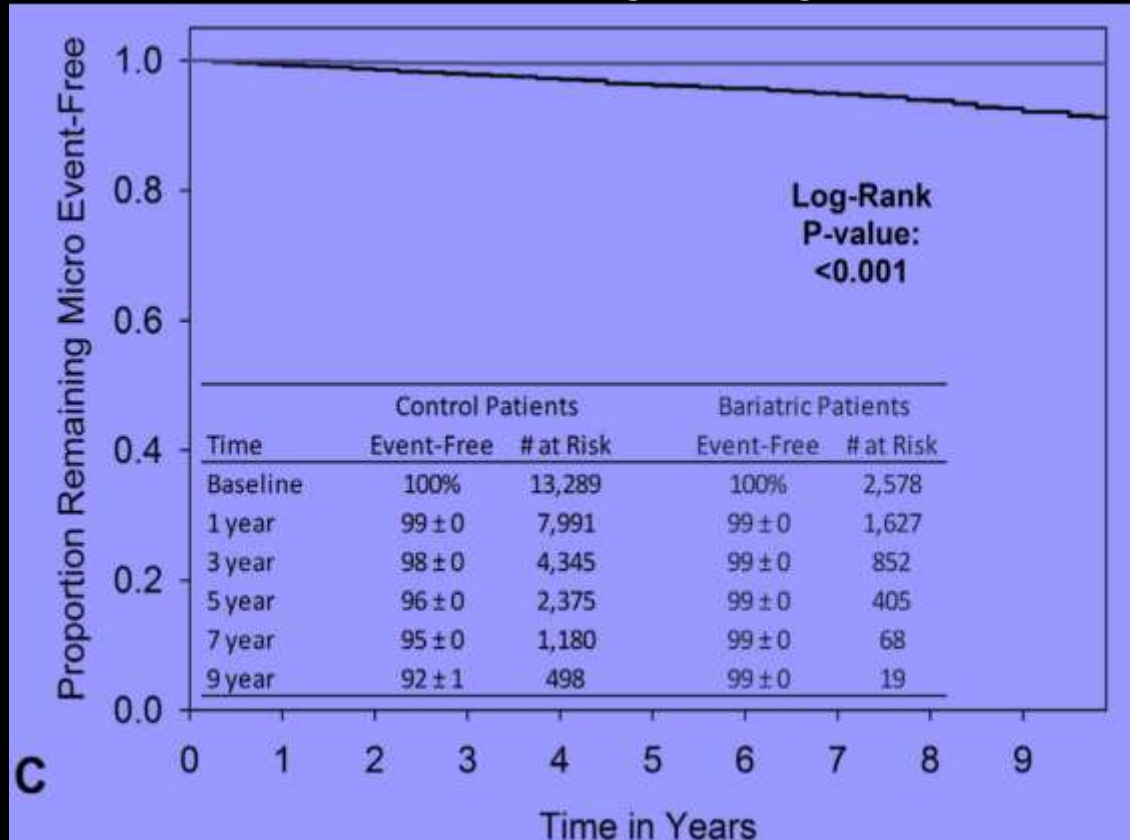
**Retinopathy – stable, worsens, improves?**

- P ,neuropathy no evidence



# Bariatric surgery and microvascular disease

Johnson et al, Journal of the American College of Surgeons, 2013, 545 - 556





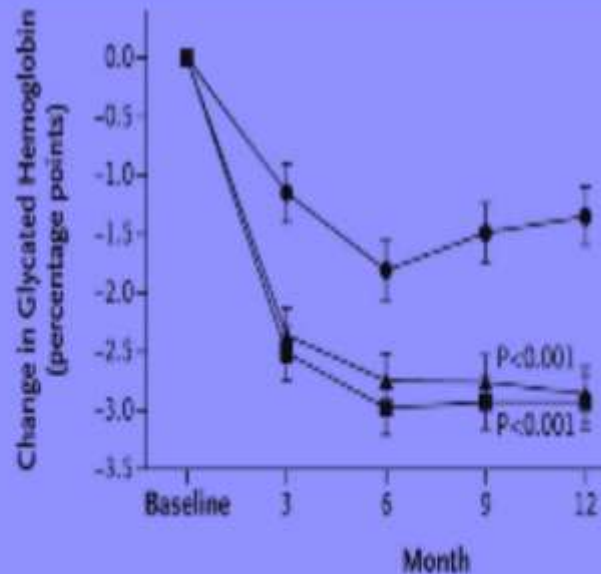
# Intense medical therapy vs bypass and sleeve

HbA1c

Tablet usage

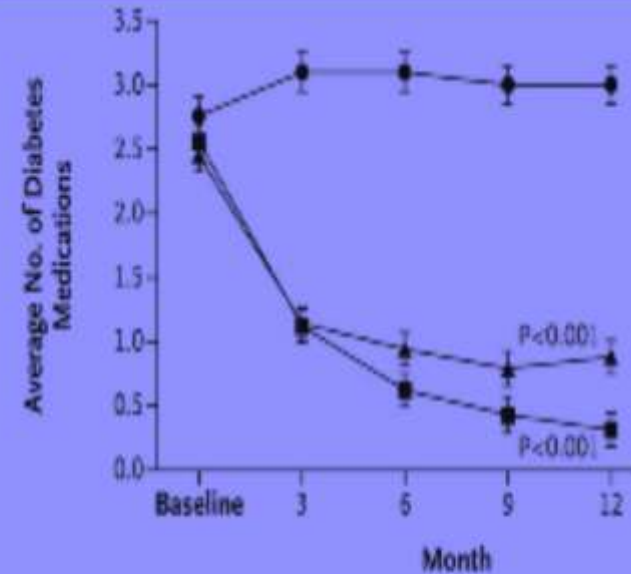
150 patients type 2 diabetes

N Engl J Med 2012; 366:1567-1576



Value at Visit

Intensive medical therapy	8.9	7.7	7.1	7.4	7.5
Roux-en-Y gastric bypass	9.3	6.8	6.3	6.4	6.4
Sleeve gastrectomy	9.5	7.1	6.7	6.7	6.6



Value at Visit

Intensive medical therapy	2.8	3.1	3.1	3.0	3.0
Roux-en-Y gastric bypass	2.6	1.1	0.6	0.4	0.3
Sleeve gastrectomy	2.4	1.1	0.9	0.8	0.9



- Post-op care
- Diet
- Psychology
- Diabetes
- Band adjustments
- Supplements
- Complications
- 

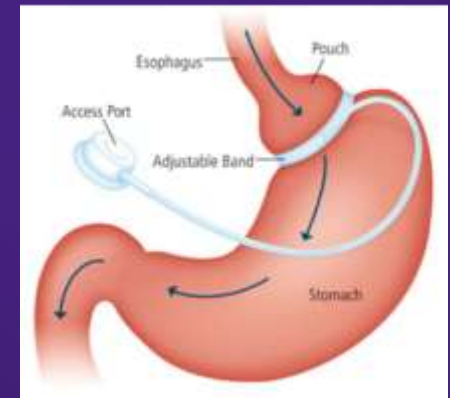
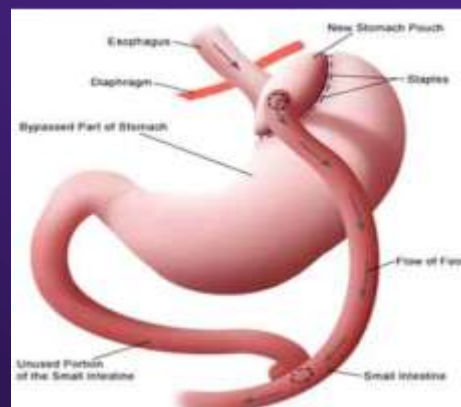
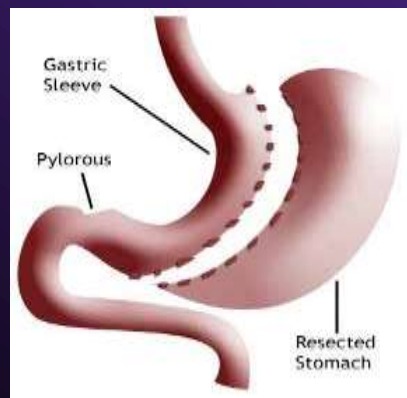




University  
of Glasgow

## Medium term complications

- LAGB – 20% band slippage and/or pouch dilatation
  - RYGB – 4.4% intestinal obstruction
    - 5-10% chronic dumping syndrome
    - Bacterial overgrowth
- Nutritional deficiencies
- Psychological





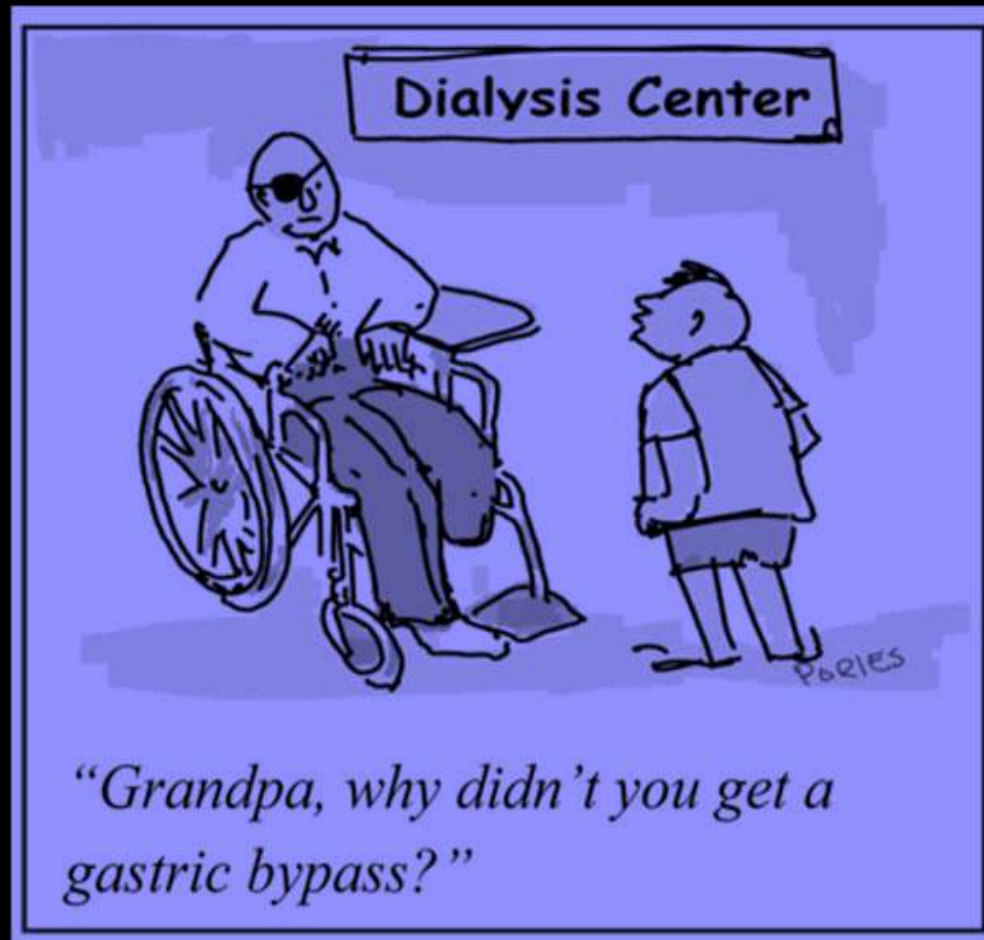
- Bariatric surgery
  - Improves glycaemic control
  - Decreases medication use
- Serious complications rare but costly
- Long term complications are unknown
- Future studies – which patients benefit?



**Weight gain/obesity**



# Surgery better than Medical therapy?



**WHAT ABOUT**

**NEW  
TECHNOLOGIES**

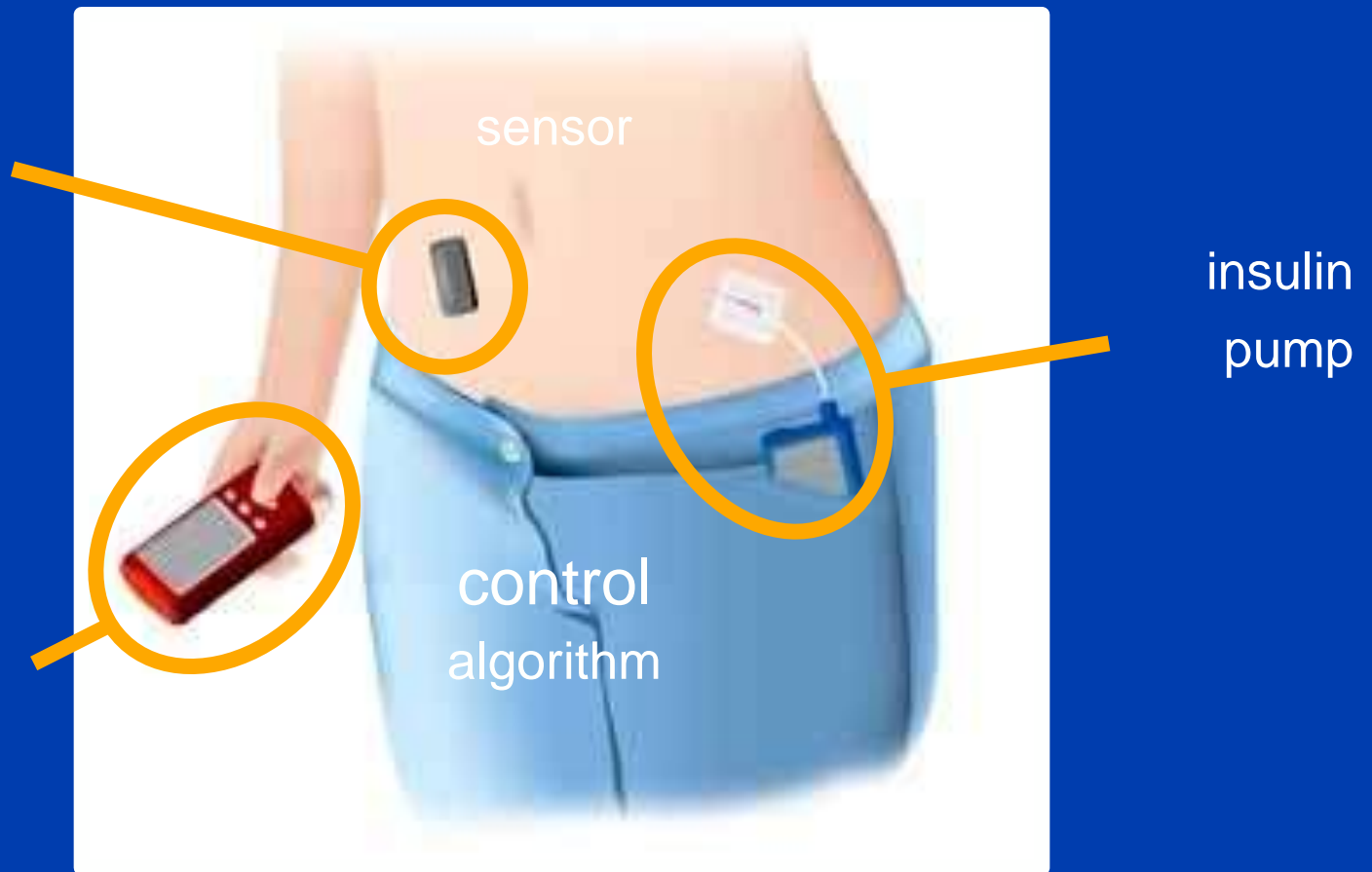




**Closed loop results**

# The artificial pancreas

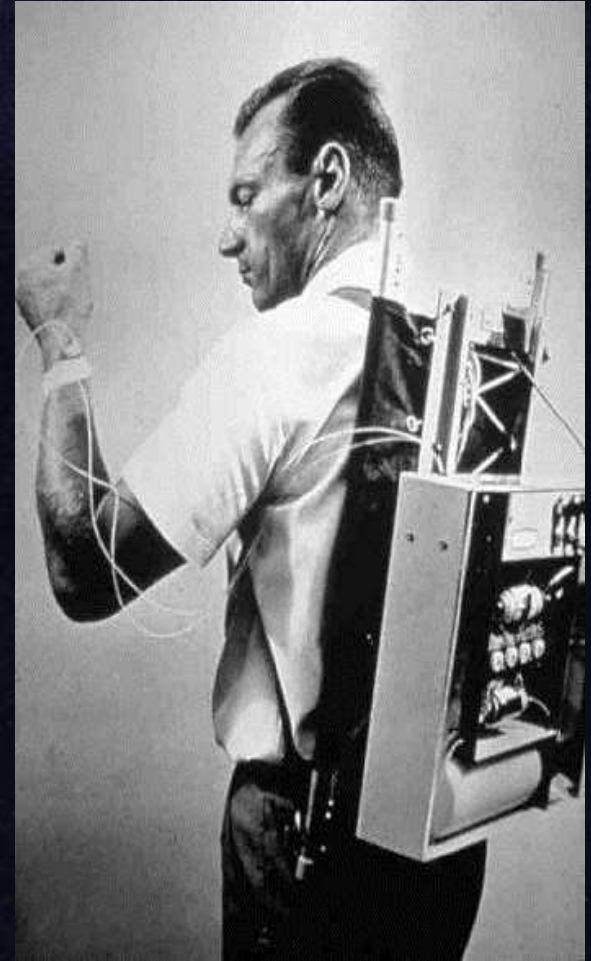
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# ***HISTORY OF INSULIN PUMPS***

First introduced in the  
**1960's** by a Los Angeles  
Physician named **Dr.**  
**Arnold Kadish.**



**1978**

- First commercially available portable insulin pump called the Autosyringe “Big Blue Brick”.





1983

- Medtronic releases the first small programmable insulin pump into the market.



# 5 years of clinical research centre studies

- Population:
  - 60 young people (6-18yrs)
  - 78 adults
  - 24 pregnant women
- 11 studies:
  - six overnight
  - three 24h
  - two 36h (adolescents)
- ~ 3,000 hours of closed-loop operation

Hovorka *et al*, *Lancet* 375: 2010

Hovorka *et al*, *BMJ* 342 : 2011

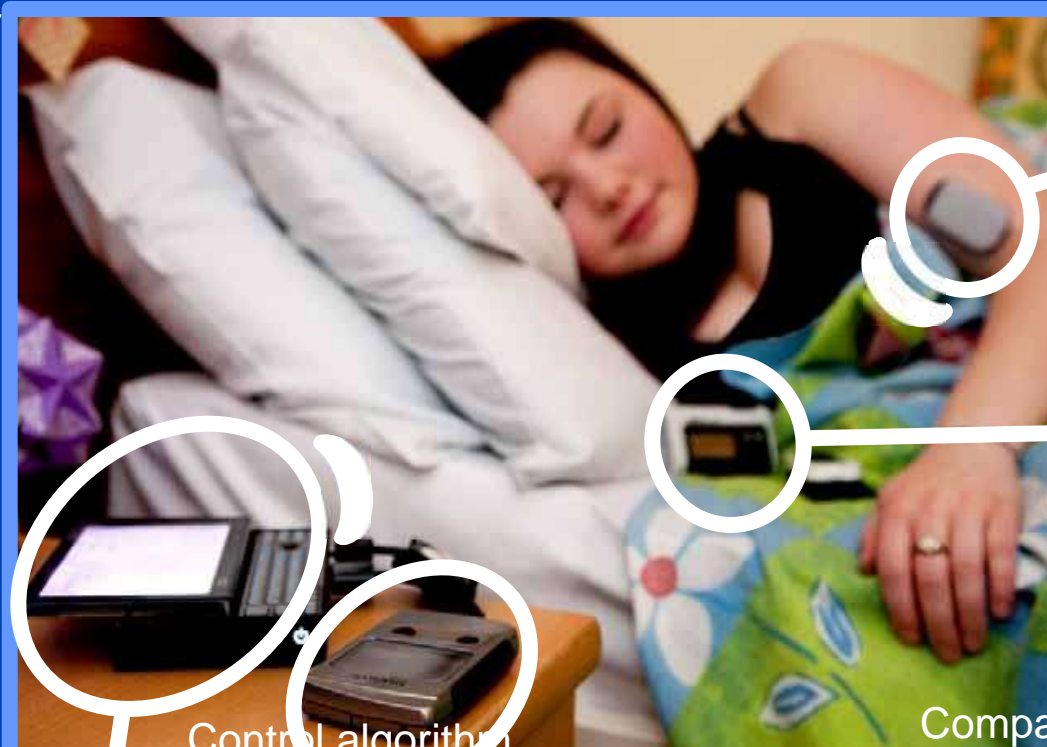
Murphy *et al*, *Diabetes Care* 34: 2011

Murphy *et al*, *Diabetes Care* 34: 2011

Elleri *et al*, *Diabetes Care* 36: 2013

# Florence prototype

Navigator  
transmitter



Dana R  
insulin pump

Control algorithm

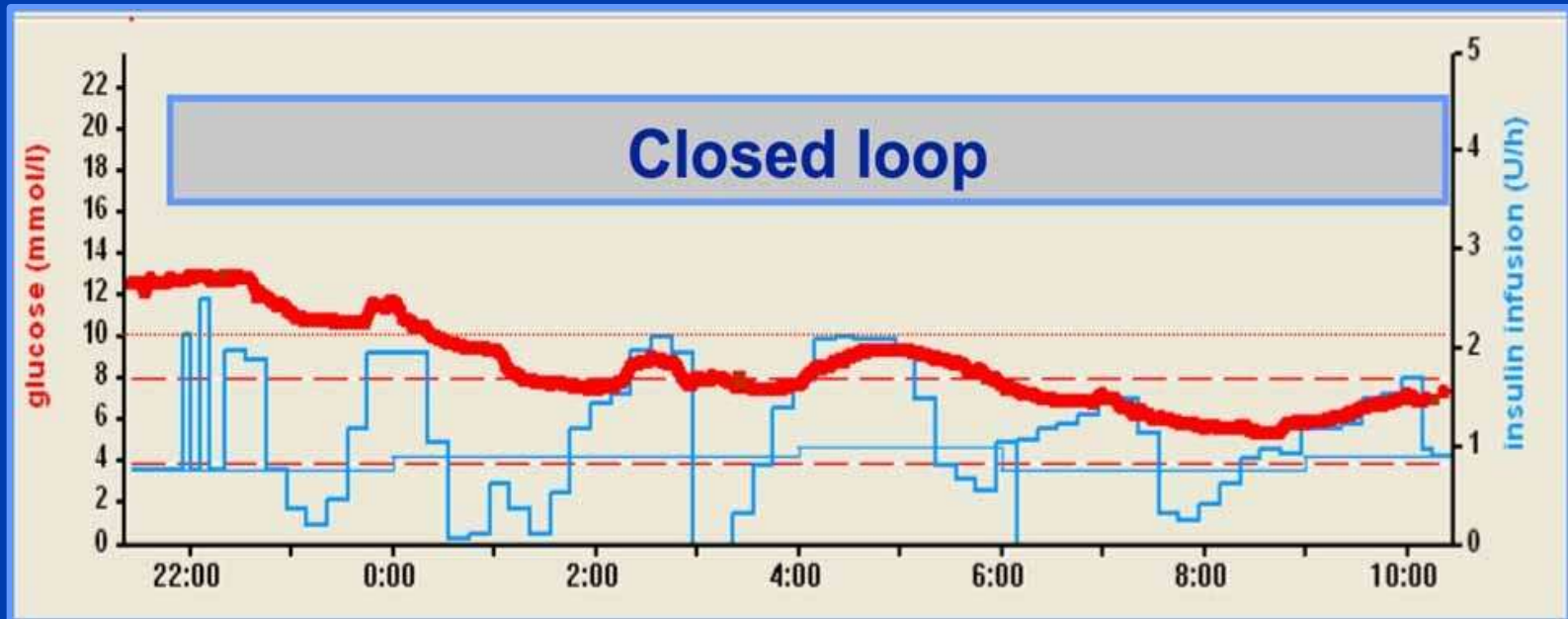
Companion

receiver

Elleri et al, *Pediatric Diabetes* 13: 2014



# Adolescent – first night on closed loop



# Florence during day-and-night use



Leelaratna *et al*, *Diabetes Care* 2014 (in press)

# Next generation closed loop prototype



# "Digital Diabetes"







# PANCREATIC TRANSPLANTATION

- Solid organ pancreas transplantaion
  - Simultaneous pancreas + kidney (SPT)
  - Pancreas after kidney (PAK)
  - Pancreas transplant alone (PTA)
- Islet transplanta on
  - Islet alone
  - Islet after kidney

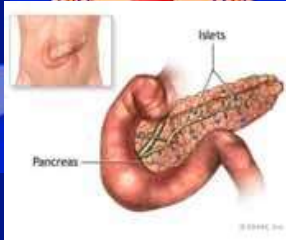
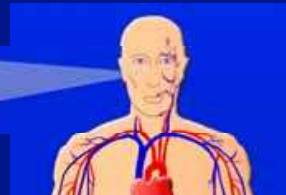
**TO WHOME??????**



# Diabetic Complications

## Diabetic Retinopathy

Blindness  
25 patients/week.



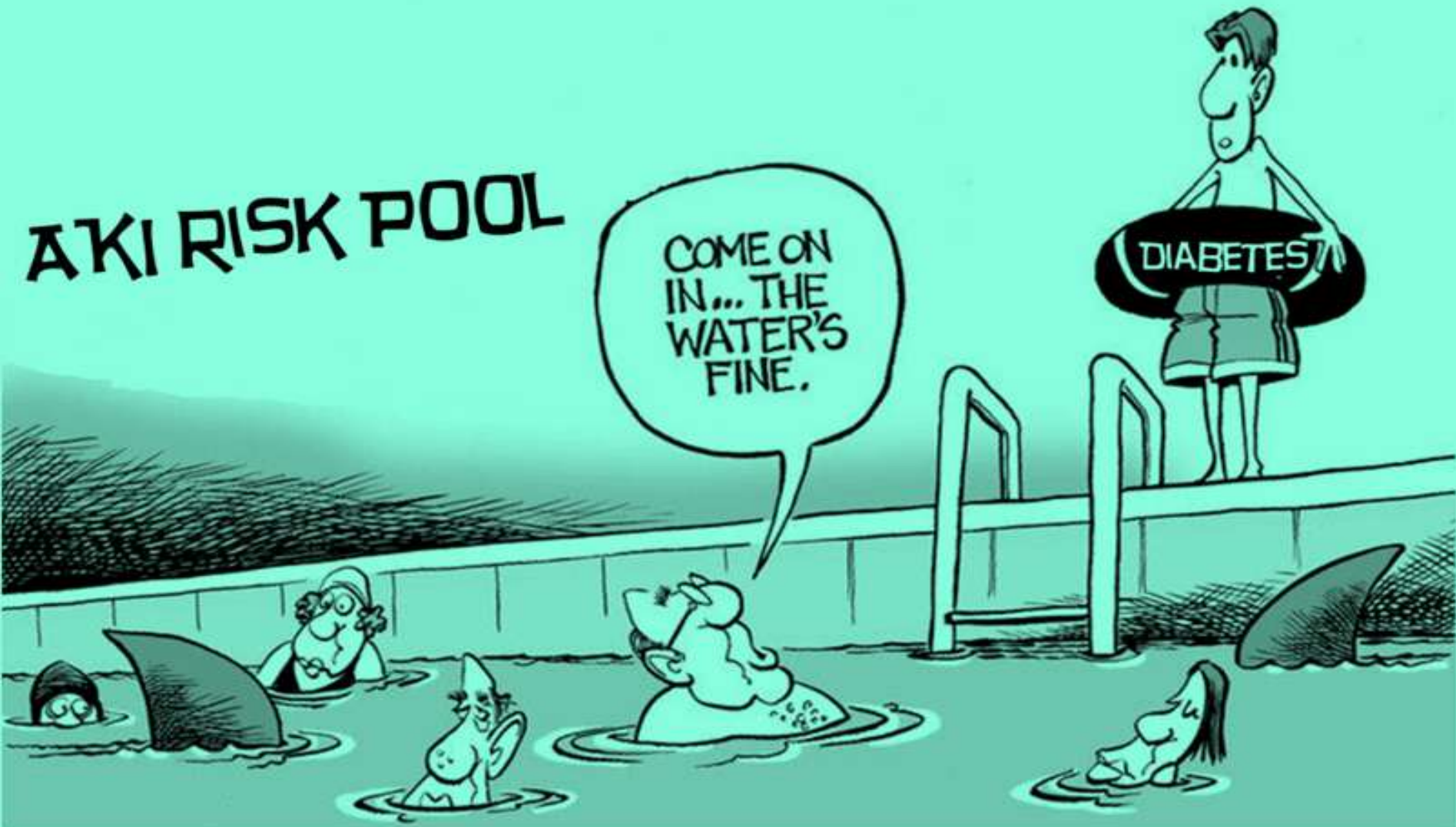
## Diabetic Neuropathy

107  
amputations/week

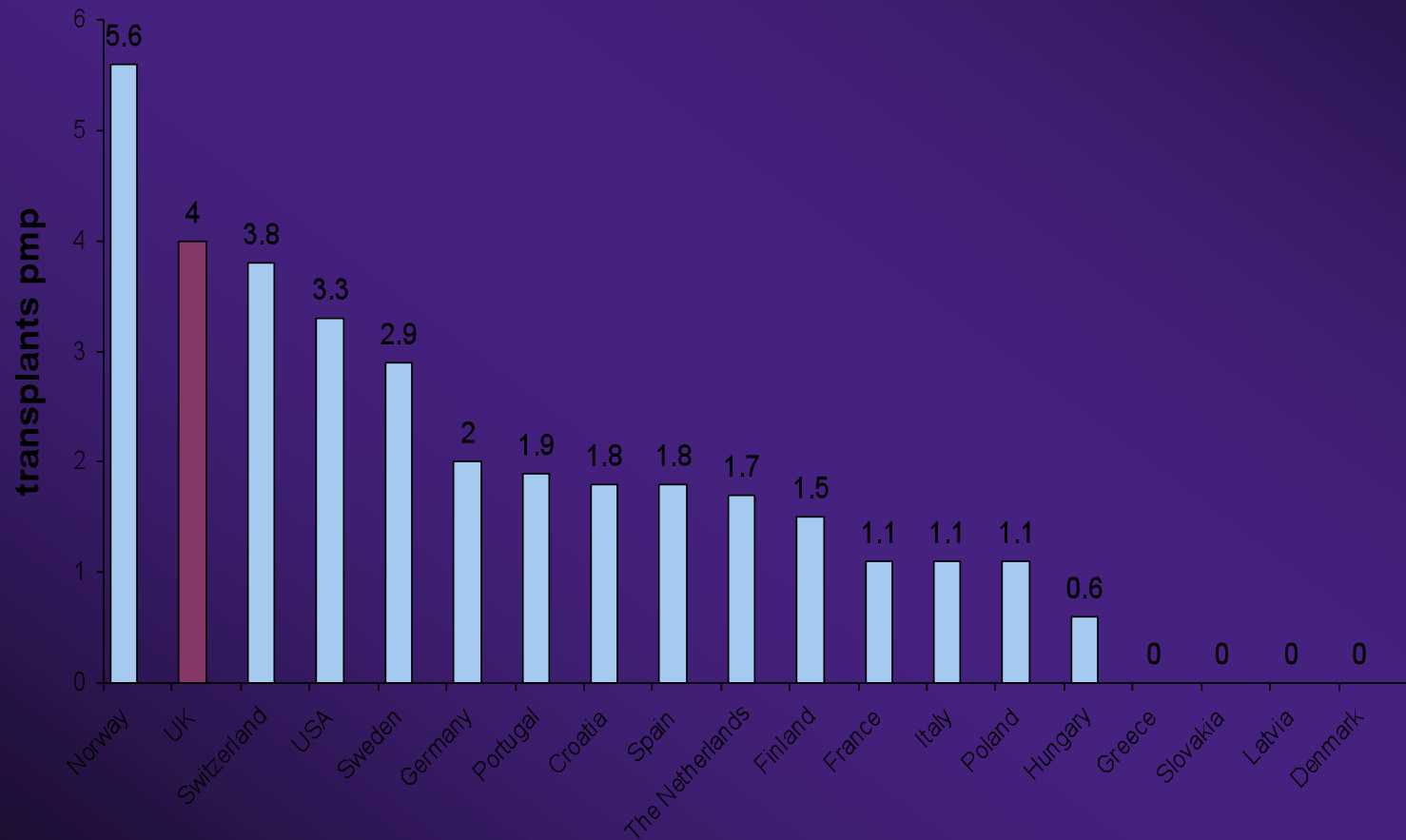




# So How Big Is The Risk In Diabetes?



# Pancreas transplant rates



Source: Council of Europe –

Transplant Newsletter

2013



# Conclusions

Stable UK pancreas transplant activity

Treatment of choice for most diabetic patients with renal failure

Results of PTA still inferior

Management of high risk

donors and recipients

challenging

indications likely to increase



# Reversal of diabetic nephropathy: lessons from pancreas transplantation

Paola Fioretto<sup>1</sup>, Michael Mauer<sup>2</sup>

<sup>1</sup> Department of Medicine, University of Padova Medical School, Padova - Italy

<sup>2</sup> Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota - USA

## Conclusion

- The human kidney has the potential to obtain a substantial architectural remodeling of the glomerular and tubular structures toward healing

WHAT ABOUT

PREVENTION  
WORKS!

IN UK

# Diabetes Prevention Program (DPP)

The DPP was a major clinical trial to determine whether diet and exercise or the oral diabetes drug metformin could prevent or delay the onset of type 2 diabetes in at risk subjects with IGT.

**YES IT DOES!!!**



# Diabetes in women - pregnancy



3/6/14



## The evidence to date

- Women with a history of GDM are at greatly increased risk of Type 2 Diabetes and recurrence of GDM or type 2 diabetes in future pregnancies
  - O'Sullivan and Mahan, *Diabetes*, 1964; MacNeill S et al. *Dia Care* 2001;24:659-662
- Life style intervention with exercise and weight management can lower The prog of IGT to type 2DM



# BMI SCORING!!!!!!!

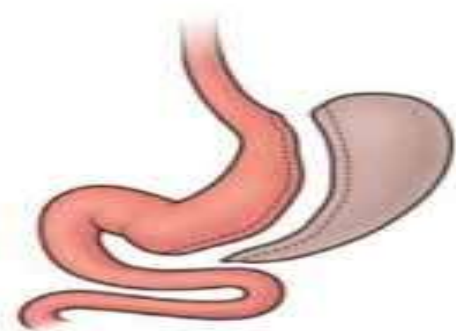
**Adjustable  
Gastric Band  
(AGB)**



**Roux-en-Y  
Gastric Bypass  
(RYGB)**

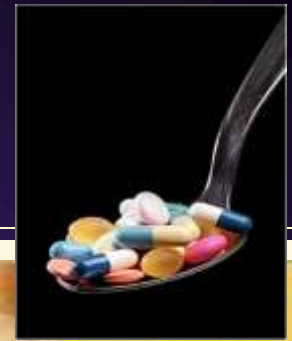


**Vertical Sleeve  
Gastrectomy  
(VSG)**



Adapted from an illustration by Walter Pories, MD, FACS

# WHAT ABOUT NEW MEDICATIONS??????



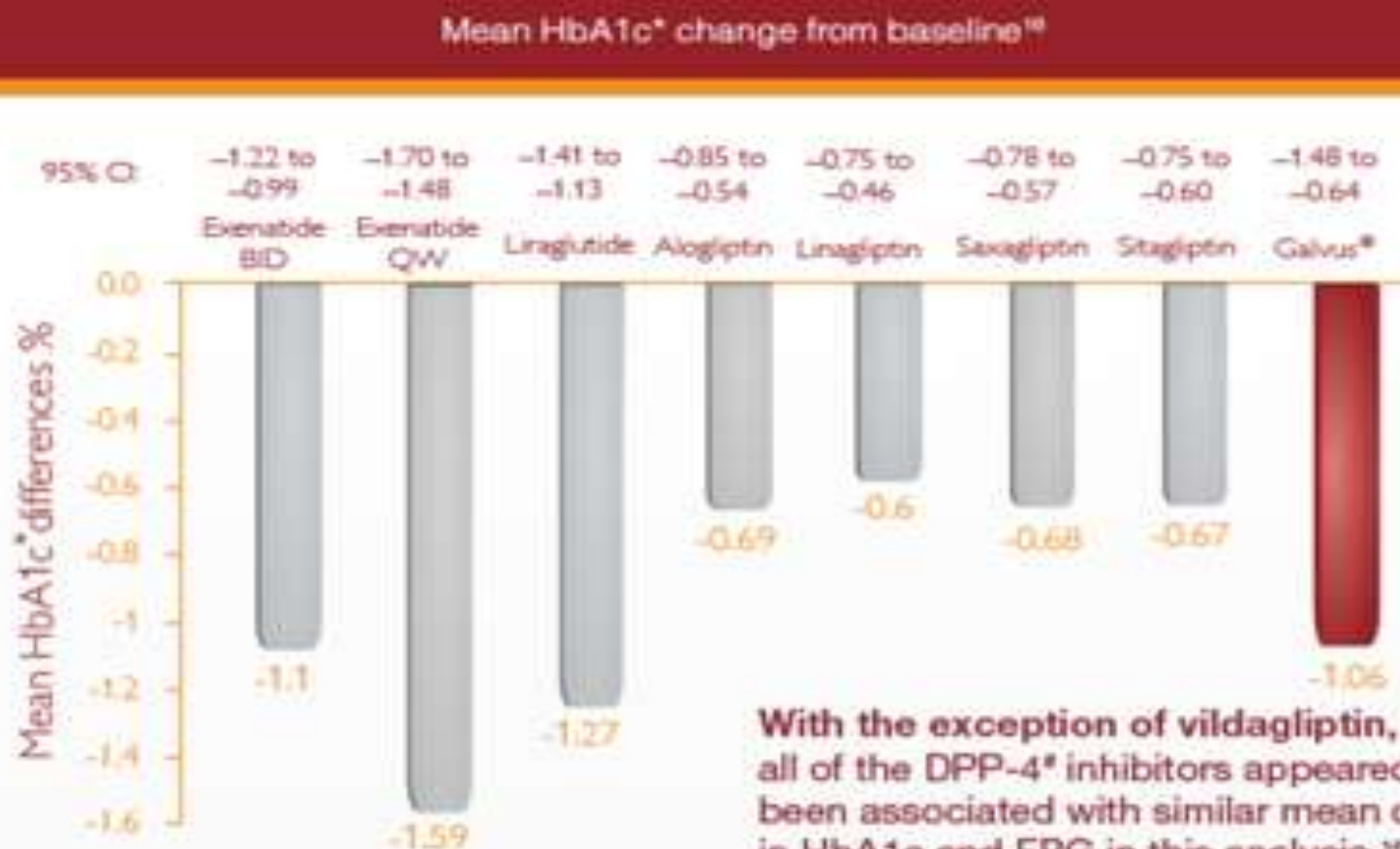
# DPP4 INH SAFETY???





# Aroda MetaAnalysis

Efficacy you can see in reducing HbA1c\* among other incretin based therapies



# Sitagliptin Improves Hepatic Functions

	baseline	4 weeks	8 weeks	12 weeks	16 weeks
AST	44.1 ± 22.0	36.5 ± 18.9***	34.1 ± 20.4***	32.9 ± 20.2***	30.6 ± 19.3***
ALT	55.6 ± 26.9	43.7 ± 21.9***	40.1 ± 23.2***	39.3 ± 22.3***	35.9 ± 22.6***
γ-GTP	60.6 ± 31.9	53.8 ± 34.0*	49.8 ± 33.3**	46.5 ± 28.2***	43.2 ± 26.1***
BMI	26.7 ± 5.30	26.8 ± 4.89	26.9 ± 4.84	26.8 ± 4.87	26.8 ± 4.84
HbA1c	8.12 ± 1.81	7.52 ± 1.16**	7.19 ± 1.07**	6.98 ± 1.00***	6.81 ± 0.93***

## Conclusions

- When added to standard of care in patients with T2DM at high CV risk, **saxagliptin** neither reduced nor increased the risk of the primary composite endpoint of CV death, MI, or ischemic stroke.



The **cardiovascular** outcome trials involving DPP-4 inhibitors have demonstrated

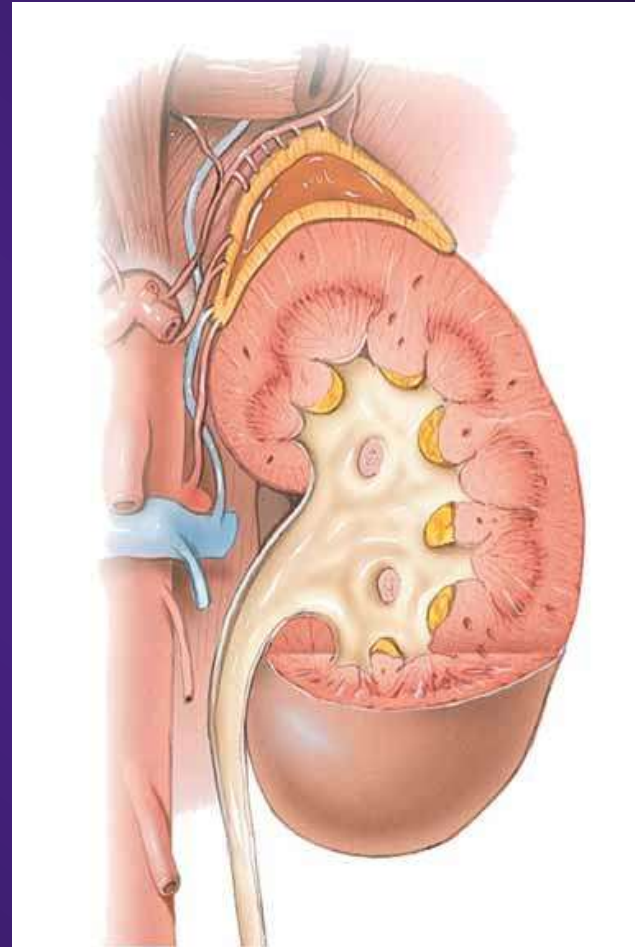
- no difference in major CV events
  - a modest but clinically relevant improvement in HbA1c despite a double blind design
  - Increase **HF** hospitalization in some cases
- **lack** of sure evidence about pancreatitis or cancer
  - **SURE** we need time!!!!!!!!!!!!!!

**OMNIGLPTIN CARRY UP GOOD NEWS**



## Role of the kidney in glucose homeostasis

- Contributes up to 20% of gluconeogenesis (more post-prandially)
- Accounts for about 10% of total body glucose utilisation
- Filters and reabsorbs up to 180g of glucose per day



# New Oral Options

- Sodium-Glucose cotransporter 2 (SGLT2) inhibitors
  - Lowers blood glucose by decreasing the amount of glucose re-absorbed by the kidneys
- Canagliflozin (Invokana®)
  - Moderate A1C reduction and weight reduction
  - Low incidence of hypoglycemia
  - Renal monitoring and dose adjustment

# Canagliflozin (Invokana®)

- **Approved for treatment of adults with type 2 Diabetes in conjunction with lifestyle interventions**
  - **Initiate at 100 mg daily, before first meal of the day**
  - Can increase to 300 mg daily if  $\text{eGFR} \geq 60 \text{ mL/min}$  (if less max dose = 100 mg/day)
- **Contraindicated with hypersensitivity, ESRD, dialysis**
  - Avoid or discontinue if  $\text{eGFR} < 45 \text{ mL/min}$
- **Additional Warnings include:**
  - Hypotension, hyperkalemia, hypoglycemia, mycotic genital infections, and increased LDL cholesterol

– the twin problems in T2DM are:

- Poor response of liver to insulin despite high fasting insulin levels

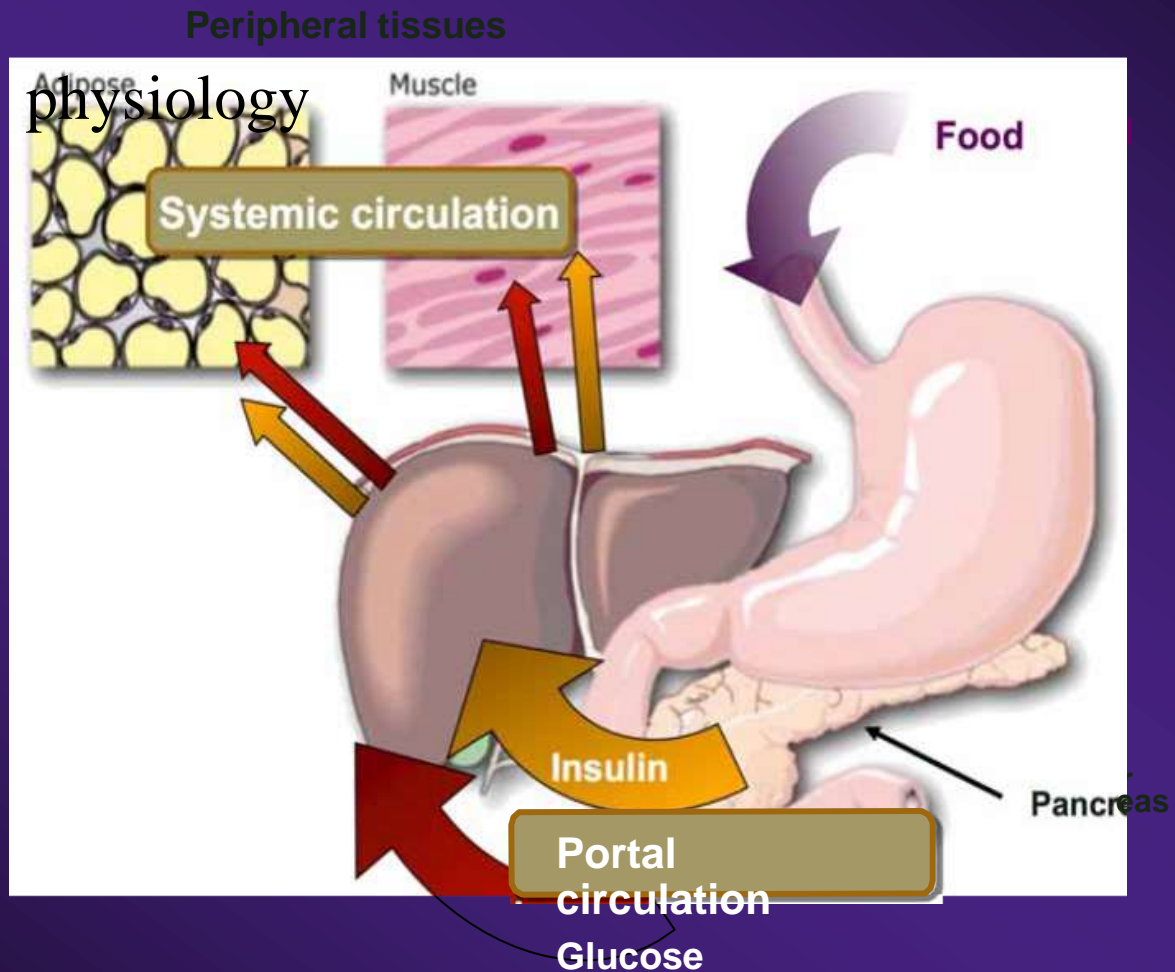
Liver insulin resistance

- Absence of rapid insulin secretion on eating

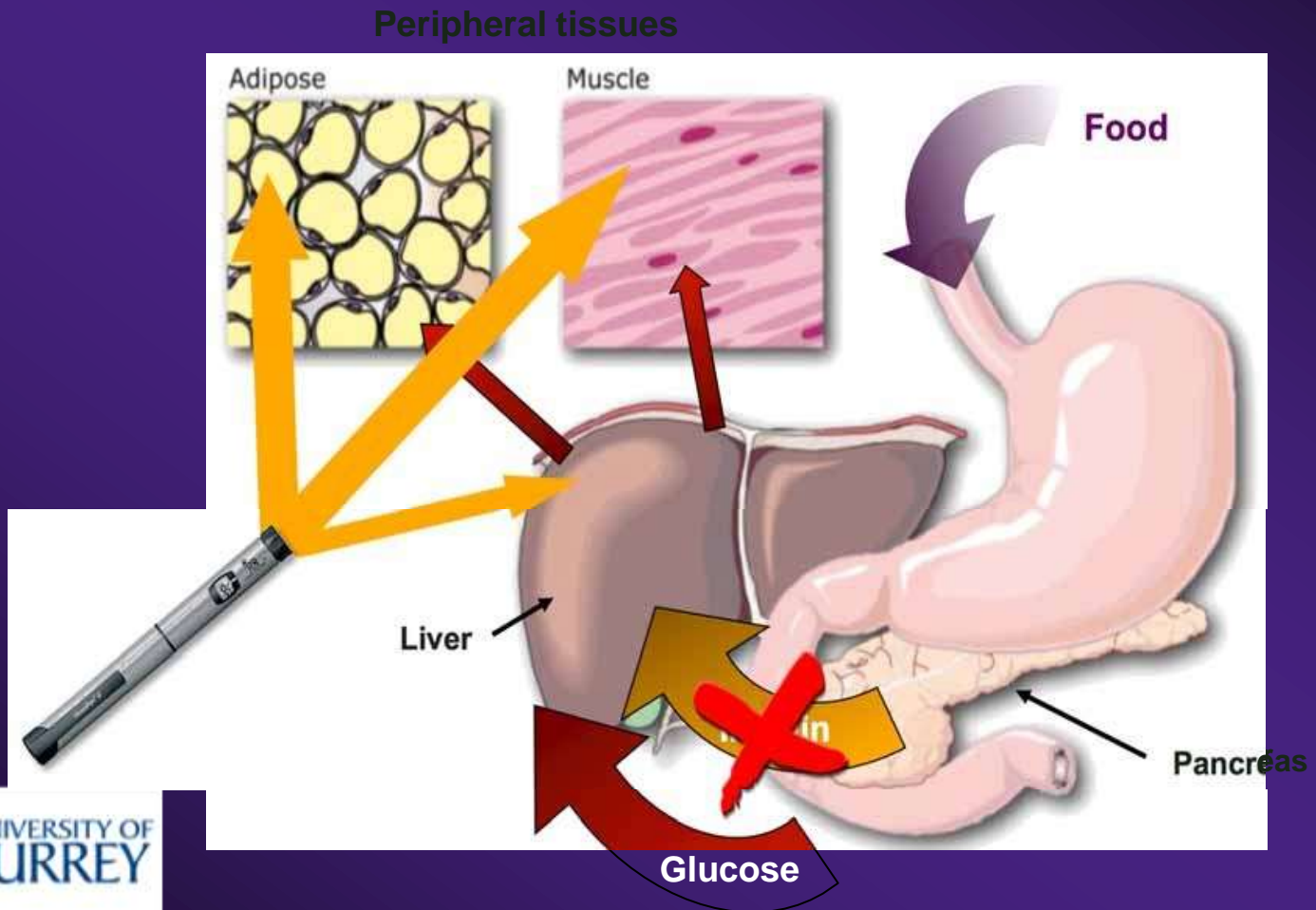
Pancreas beta cell problem



# Insulin Distribution In Normal physiology



# Insulin Distribution In exo





# New Insulins



## Basal Insulins (Long acting)

Degludec (Novo Nordisk)

– Bil (Eli Lilly)  
(LY2605540)

– Biosimilar Glargine Eli Lilly



# Ultra-long Acting Insulin?

- Insulin Degludec
  - Proposed to have > 24 hour activity to give better once daily dose coverage than other products
    - Half-life ~ 42 hours
- FDA declined to approve as of Feb 2013
  - Requested more long term cardiovascular safety data from dedicated trial
- **Has been approved in the European Union and uk late 2013**



# New Insulins

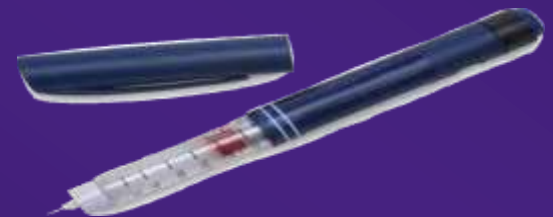
- **Rapid Acting Insulins**

- FIAasp NN 1218

(Novo Nordisk)

- Humalog U200

(Eli Lilly)



## New Insulins

- Combinations
  - Degludec with Liraglutide  
**IDegLira** (Novo Nordisk)
  - Glargine with Lixisenatide  
**LixiLan** (Sanofi)



UPCOMING!!!!

## Phase 1

3 oral insulins

Hepatoselectiv insulins

– By a range of companies

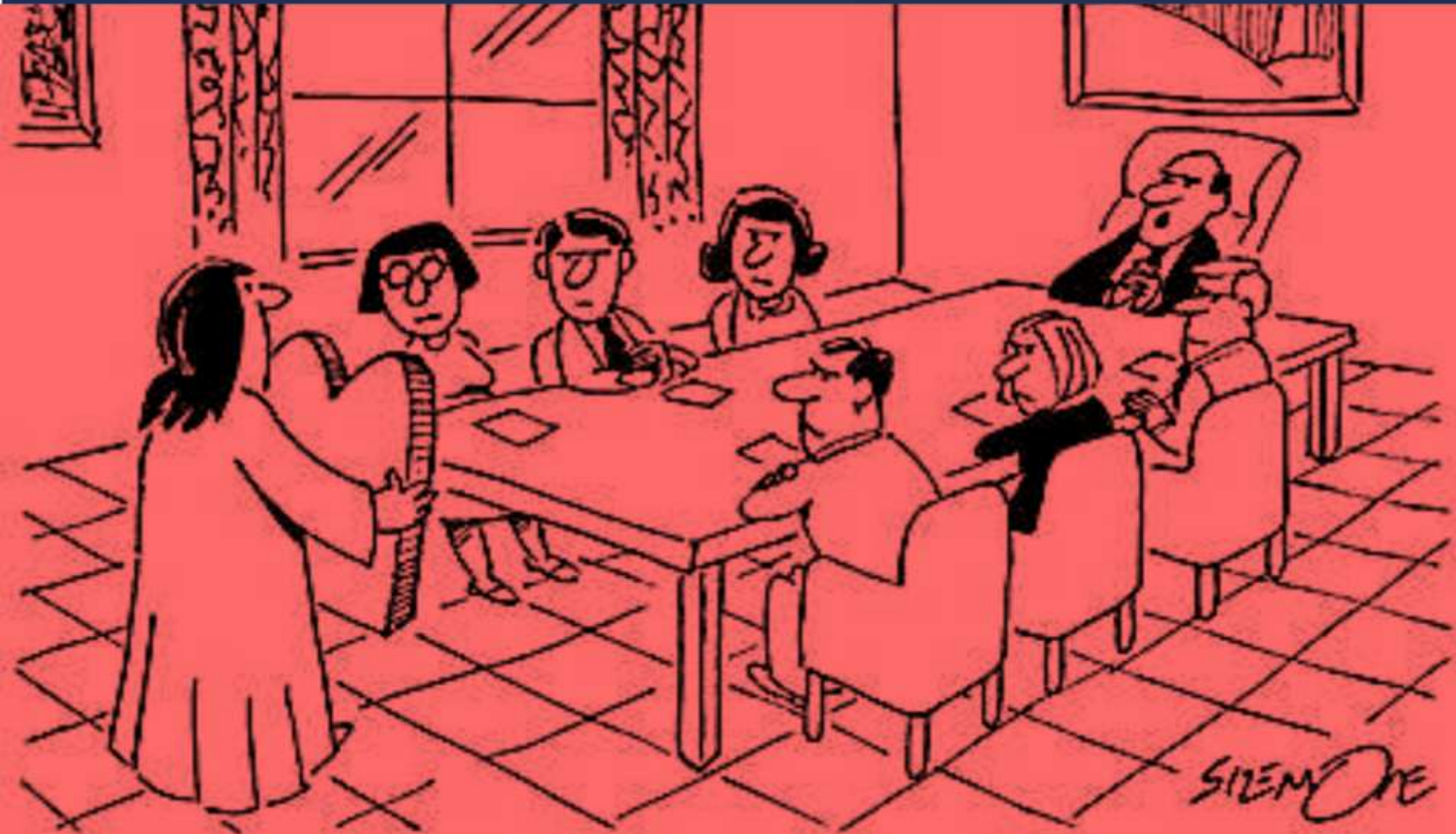


# Injectable Medication RECENT Options

- **Glucagon-like peptide - 1 receptor agonists**
  - Exenatide, liraglutide
  - Albiglutide - may be next agent in class (FDA petition submitted by GlaxoSmithKline Jan 2013); proposed for once weekly injection
- **Amylin mimetics**
  - Pramlintide - use with insulin; mostly in patients with type 1 DM



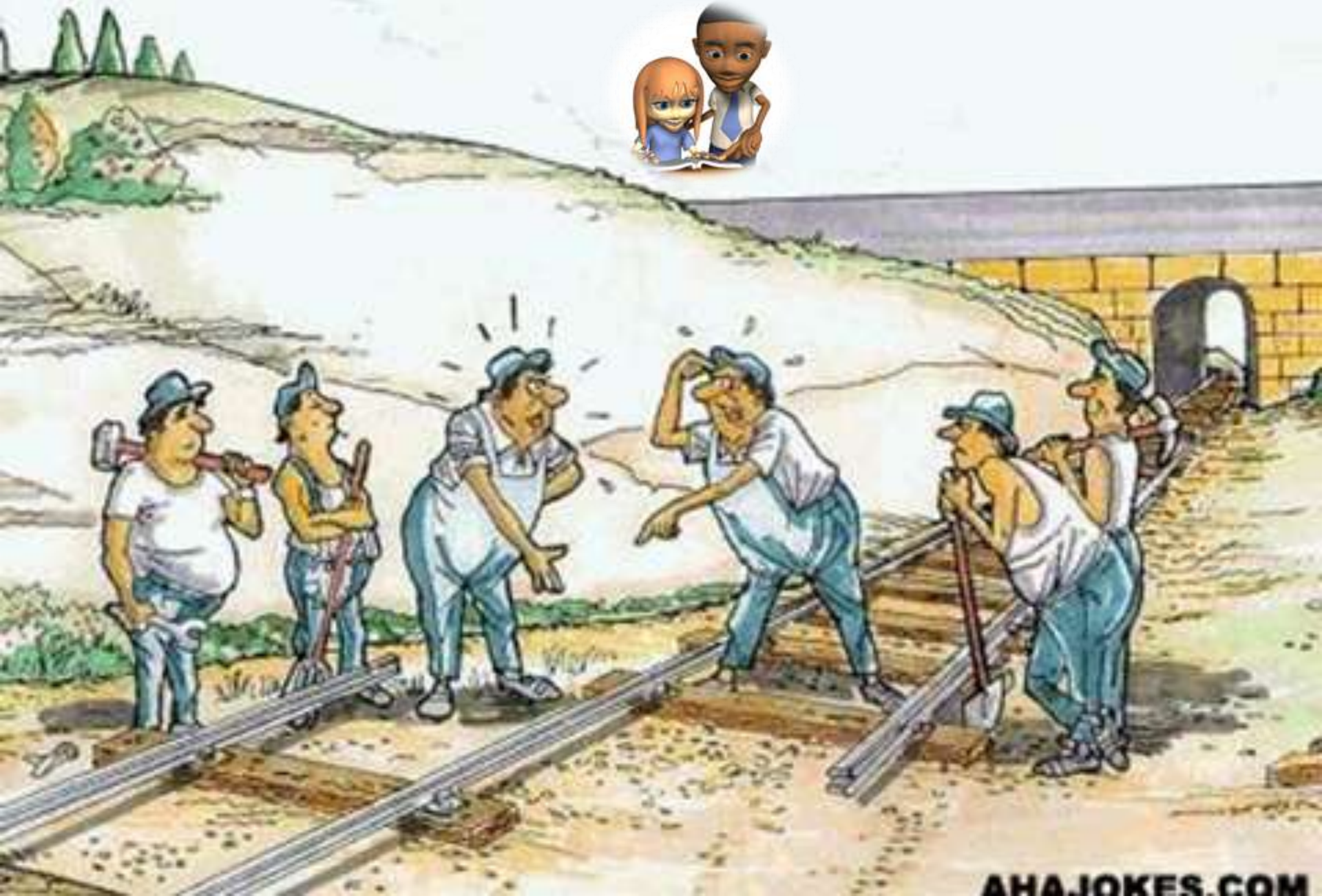
# We'll think about it.....







# Team Work





Thank you ...



Thank You

obrigado

Dank U

Merci

mahalo

Köszí

спасибо

Grazie

Thank  
you

mauruuru

Takk

Gracias

Dziękuję

Děkuju

danke

Kiitos